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Optimizing Treatment Strategy for hepatocellular carcinoma
주요 암의 5년 생존율 추이: 전체

<table>
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<tr>
<th>년도</th>
<th>위</th>
<th>갑상선</th>
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* 담낭 및 기타담도
Nationwide Survey of HCC in Korea
- 5 Years Survival Rate -

According to Tumor Size

- < 2 cm
- 2 - 4.9 cm
- 5 - 9.9 cm
- >= 10 cm
Introduction

• The timing of the diagnosis substantially governs the type of treatment.
• When diagnosis is made early, the treatment has curative intent.
• However, when diagnosis is made at a late stage, treatment may be palliative.
• Most Asian patients with HCC are advanced status at diagnosis.
• Recently, there are emerging trends to improve the management of HCC.
What is optimal treatment?

• Right treatment at right time
• Select right patient
• Maximize therapeutic efficacy and minimize risk and patient’s burden
적절한 치료 위해 고려사항

- 치료대상자; 병기, 간기능 및 환자 상태(PS, 나이, 경제력)
- 치료법; 효과, 부담, 시술자 숙련도, 보험적용여부
- 치료전 상태의 적절한 평가
- 치료후 치료반응의 효과판정 평가 및 추적관찰
How to win (知彼知己, 百戰百勝) (孫子兵法)

1. Know enemy (知彼);
2. Know myself (知己);
3. Establish good strategy (必勝戰略, roadmap)
Characteristics of HCC

• Tumor neovasculature and frequent vascular invasion with intra-and extra-hepatic metastasis

• Great heterogeneity with respect to tumor behavior

• Frequent association with different status of the underlying liver cirrhosis and viral hepatitis
Treatment Options for HCC

- Radical therapies (40%)
  - Surgical resection
  - Liver Transplantation (CLT/LDLT)
  - Local ablation therapy

- Palliative therapies (40–50%)
  - Transarterial embolization/ Chemoembolization
  - Molecular target therapy (sorafenib)
  - Hormonal treatments/ Immunotherapy
  - Antiproliferative agents
  - HAIC
  - Others; pilot therapy; Radiotherapy; external, internal RT, etc
  - Combination therapy

- Symptomatic treatment (10–20%)
Staging Systems of HCC

- To predict the prognosis
- To stratify the patients according to prognostic variables in the setting of clinical trials
- To guide therapeutic approach
Data from 1,437 HCC patients who were managed in YLCSC for the first time (From Jan. 2003 to Dec. 2007)

<table>
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<th>Stage</th>
<th>No. (%)</th>
<th>Median</th>
<th>6-MOS</th>
<th>1-YRS</th>
<th>2-YRS</th>
<th>3-YRS</th>
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TNM stage; LCSGJ, AJCC

(Stage I)  (Stage II)  (Stage III)  (Stage IV)
BCLC Treatment Overview: Linking Staging to Treatment

- **HCC**
  - **Early Stage**
    - Surgical Treatment
    - Local Ablation
    - (30%) Potentially Curative Treatments 5–y Survival: 40%–70%
  - **Intermediate Stage**
    - TACE
  - **Advanced Stage**
    - sorafenib
    - (50%–60%) Randomized Trials
      - Median Survival If Untreated: 6–16 mo
  - **End Stage**
    - BSC
    - Survival <3 mo

TACE = transarterial chemoembolization; BSC = best supportive care.

Liver Function & Tumor Stage

- Child-Pugh Class

\[ P < 0.001 \]

- TNM Stage (UICC v.6)

\[ P < 0.001 \]
Cause & Treatment

• Associated Disease

• First Treatment

$P<0.001$

Random Voluntary

Random Voluntary

Systemic Tx
EBRT
Transarterial Tx
Local Ablation
LT
Resection

대한간암연구학회 간암등록사업
치료법 선택의 기준

- 기성복형 치료법
- 개인 맞춤형 치료법
- 현 guideline은 나라 별, 개인별 특수 입장 을 충분히 고려하기 어려움
- 객관성 부족 및 일반 화의 문제점
How to establish guideline?

- Evidence based guideline; Level of evidence 1; RCT
- Clinical experienced based guideline; Level of evidence 2,3; case control
AASLD Practice Guideline: BCLC Staging and Treatment Strategy

HCC

Very early stage
- single HCC mass <2 cm carcinoma in situ

Early stage
- 1 HCC or 3 nodules <3 cm, PS 0

Intermediate stage
- No portal vein thrombosis
- Multinodular, PS 0

Advanced stage
- Portal invasion, Metastases, PS 0-2

Terminal stage

Potentially curative treatments
- Resection
- OLT
- PEI/RFA

Palliative treatments
- Chemoembolization
- Sorafenib

Symptomatic therapy

(30%)
50%-70% 5 years

(50%)
10%-40% 3 years

(20%)

Lovett et al, 2008
Cosensus-based Treatment Algorithm for HCC
(Japan Society of Hepatology 2007)

Extrahepatic Spread

Liver Function

Vessel Invasion

Number

Size

Treatment

Intensive follow-up
Ablation

Resection Ablation

Resection TACE (TACE+ Ablation)

TACE TAI (Resection • Ablation)※5

LT

Resection TAI※7

TACE※8

Transplantation (Experimental Treatment) ※9

Palliative care

Hypovascular
Early HCC ※3

≤ 3cm

> 3cm

Within Milan criteria and Age ≤ 65

Exceeding Milan criteria and Age > 65

Within Milan criteria and Age ≤ 65

※1, 2

Kudo M, Okanoue T. Oncology 2007: 72; 2-5
APASL guidelines

HCC

Confined to the liver
Main portal vein patent
Resectable

Yes
Resection/RFA (for < 3 cm HCC)

Solitary tumor ≤ 5 cm
≤ 3 tumors ≤ 3 cm
No venous invasion
Child–Pugh A
Local ablation

Child–Pugh B
Transplantation

Child–Pugh C
TACE

No
Sorafenib or systemic therapy trial

Extrahepatic metastasis
Main portal vein tumor thrombus
Child–Pugh A/B
Child–Pugh C

Tumor > 5 cm
> 3 tumors
Invasion of hepatic / portal vein branches
Child–Pugh A/B
Supportive care

Child–Pugh C
HCC Practice Guideline
-KLSCG/KNCC-

• 2003: 1st version
• 2009: 2nd version
• Evidence based approach
• Cooperation – physician, surgeon, radiologist, pathologist, radiation oncologist, medical oncologist
Treatment Algorithm (KLCSG/KNCC)

Hepatocellular carcinoma → Tumor treatable
- TNM stage (modified UICC by LCCGJ)
- Child-Pugh class
- ECOG performance

Optional test:
- ICG test
- Bone scan
- Chest CT
- Angiography
- 18F-FDG PET-CT
- Volume measurement
- Gastric endoscopy

Tumor treatable → Curative treatment
- Hepatic resection (II)
- Liver transplantation (II)
- Radiofrequency ablation (I)
- PEIT (II-1)

Tumor treatable → Non-curative treatment
- TACE (I)
- Radiation therapy (II-1)
- Chemotherapy*
  * Sorafenib (I), Cytotoxic agents (III)

Tumor untreated
- Far advanced tumor stage
- Decompensated liver functions (Child-Pugh class C)**
- Compromised performance (ECOG >2)
- Accompanied uncontrolled systemic disease

Tumor untreated → Best supportive care

**considering liver transplantation (I)

Clinical trial:
- Drug eluting bead-TACE
- Radioembolization
- HIFU
- Hepatic arterial infusion chemotherapy
- Cytotoxic chemotherapy
- Metastatectomy
Nation-wide Survey of HCC in Korea - Frequency of 1st Treatment Methods-

<table>
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<tr>
<th>Treatment Methods</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
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<td>19.2</td>
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<tr>
<td>Total: 4444</td>
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</table>
Practice Guideline: Early Stage

Very early stage
- Single HCC mass <2 cm carcinoma in situ
  - 1 HCC
  - Portal pressure/bilirubin
    - Normal
      - Resection

Early stage
- 1 HCC or 3 nodules <3 cm, PS 0
  - Possible contraindication to transplant
  - NO
  - YES
    - OLT
    - PEI/RFA

Intermediate stage
- No portal vein thrombosis
- Multinodular, PS 0

Advanced stage
- Portal invasion
- Metastases, PS

T-shirt Size

(30%)
Optimal Tx in early stage

(Stage I)  (Stage II)

Location
Age
Liver Function Status
Bleeding tendency
Emerging Trends of Management in Early Stage

- Resection; Classic or Minimal invasive surgery (laparoscopic or Robot surgery)
- Liver transplantation; expansion of criteria
- Local ablation therapy; RFA, PEIT or Holmium
- Adjuvant therapy after curative tx.; molecular target therapy (phase III; STORM), immunotherapy (phase II; ASCI)
- Combined therapy; Adjuvant therapy after curative tx.

Curative efficacy
CT (2010.05.15) - before TACE
Practice Guideline; Intermediate Stage

- **Very early stage**: single HCC mass <2 cm carcinoma in situ
  - 1 HCC
  - Portal pressure/bilirubin
  - Normal
  - Resection
  - Potentially curative treatments

- **Early stage**: 1 HCC or 3 nodules <3 cm, PS 0
  - 3 nodules ≤3 cm
  - Possible contraindication to transplant
  - OLT
  - PEI/RFA

- **Intermediate stage**: No portal vein thrombosis; Multinodular, PS 0
  - Chemoembolization

- **Advanced stage**: Portal invasion, Metastases, PS 0-2
  - Sorafenib

- **Terminal stage**

T-shirt Size:

- **S**: Length 24" Width 18" 6.5" 11"
- **M**: Length 26" Width 18" 12" 14"
- **L**: Length 28" Width 20" 14" 16"
- **XL**: Length 31" Width 22" 16" 18"
Data from 1,437 HCC patients who were managed in YLCSC for the first time (From Jan. 2003 to Dec. 2007)
TACE; Effective but incomplete
Incomplete TACE induces angiogenesis

Sergio et al., Am J Gastroenterol 2007
Hypoxia in the post-TACE tumour micro-environment leads to angiogenesis

- HIF-1α responds to hypoxia in tumour
- VEGF is a key mediator of tumour neovascularization (growth and permeability)

How to overcome incomplete TACE?

• Sequential therapy?
• Use new embolic material?
• Use more powerful killing agent?
• Combined therapy?
DC Bead VS cTACE

Overall 6-month Tumor Response Rates

\[ p = 0.11 \]

Disease Control = Objective Response + Stable Disease

Objective Response = Complete Response + Partial Response

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<th>DC Bead</th>
<th>cTACE</th>
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<tr>
<td>Objective Response</td>
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<td>52</td>
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<tr>
<td>Complete Response</td>
<td>63</td>
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Radioembolization with Yttrium-90 microspheres

Ischemia

Radiation
European (\(^{90}\)Y resin microspheres) and US (\(^{90}\)Y glass microspheres) survival data in Patients with HCC by BCLC stage

Riad Salem et al. 2010, Gastroenterology 138:1,52-64
Bruno Sangro et al. 2010, presented at ASCO GI
Rationale for Combining Locoregional Intra-Arterial Therapies With Systemic Antiangiogenic Therapy

Embolization → HYPOXIA

HYPOXIA → HIF-1α

HIF-1α → Tumor Invasion

HIF-1α → Angiogenesis

HIF-1α → Tumor Metabolism
Combined therapy

- TACE+ molecular target therapy (SPACE study)
- TACE+ LAT
- TACE+ Radiation therapy
TACE vs. TACE+RT: Survivals

TACE vs. TACE+RT
P<0.01

14.3%
36%

Response rate; 65.8%

Shim and Seong et al. 2005, Liver International
TACE vs. TACE+RT

105 pts (1992-2002) ≥ 5 cm

Lipiodol\textsuperscript{TM} 5-20 ml + Adriamycin 50 mg+gelfoam

Incomplete TACE 73 pts (69.5%)

Complete TACE 32 pts (30.5%)

TACE;35 pts

TACE+RT;38 pts

*Radiotherapy: 36-59.4 Gy (Med; 54 Gy in 1.8 Gy/fr)

Comparative analysis

Shim and Seong et al. 2005, Liver International
TACE vs. TACE+RT: Median survival-Tumor size

Shim and Seong et al 2005, Liver International
Advanced Stage
A broad spectrum of disease; vascular invasion or extrahepatic spread (single or multiple), or both
Sorafenib consistently increased overall survival in different global patient populations

**SHARP**
- Sorafenib (n=299)
  - Median OS: 10.7 months
- Placebo (n=303)
  - Median OS: 7.9 months

**HR = 0.69**

**Asia-Pacific**
- Sorafenib (n=150)
  - Median OS: 6.5 months
- Placebo (n=76)
  - Median OS: 4.2 months

**HR = 0.68**
Position of Sorafenib in HCC; AP region

Pros
- Only one approved drug therapy by large scaled prospected RCT
- Less harmful oral drug for cirrhotic liver
- Is able to manage in out-patient clinic

Cons
- High cost to maintain indefinitely tx in A-P region
- OS in Asian patients with HCC is shorter than SHARP trial
- SAE is more common
- Not enough data in clinical practice level
Survival analysis of Sorafenib in Single Center

Median PFS = 3.0 months (CI 95%, 2.6–3.4)

Median OS = 6.0 months (CI 95%, 5.4–6.6)

A total of 151 HCC pts treated with sorafenib in Severance Hospital (2007–2010)
First interim results of the global investigation of therapeutic decisions in hepatocellular carcinoma (HCC) and of its treatment with sorafenib (GIDEON) study: Use of sorafenib (Sor) by oncologists and nononcologists in the management of HCC. A. P. Venook, R. Lencioni, J. A. Marrero, M. Kudo, K. Nakajima, S. Ye; University of California, San Francisco Comprehensive Cancer Center, San Francisco, CA; Pisa University School of Medicine, Pisa, Italy; University of Michigan, Ann Arbor, MI; Kinki University School of Medicine, Osaka, Japan; Bayer HealthCare Pharmaceuticals, Montville, NJ; Zhongshan Hospital, Fudan University, Shanghai, China

Background: GIDEON is an ongoing, global, prospective, non-interventional registry study of patients (pts) with unresectable HCC (uHCC) receiving Sor under real-life practice settings. From January 2009 to September 2010, over 2,200 pts have been enrolled from 32 countries. Per protocol, the first planned interim analysis was triggered when 500 enrolled pts were followed for at least 4 mos; the primary safety and efficacy results were reported in October 2010. A preplanned subset analysis of treatment patterns across MD specialties is reported here. Methods: Demographics, medical, disease and treatment history are recorded at enrolment; Sor dose, concomitant treatments, performance status, liver function are noted at follow-up. Standard efficacy measures and adverse events (AEs) are captured. Preplanned subanalysis by MD specialty was conducted. Results: Of the 141 treating MDs, 69 (49%) were hepatologists/gastroenterologists (Hep/Gls), 55 (39%) were medical oncologists (Oncs) and 17 (12%) were other specialties. Descriptive statistics of differences in pts’ HCC stage, Sor treatment and AEs by the main specialties are shown for the 479 pts evaluable for safety (Table). Conclusions: Interim data from the GIDEON study suggests differential use of Sor by MD specialties. It appears that Oncs tend to treat with lower doses of Sor and for a somewhat shorter duration than Hep/Gls. If these data persist, it will be important to explore the reasons for these differences in Sor usage between Oncs and Hep/Gls and potential impact on patient outcomes.

<table>
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<tr>
<th>Pts treated</th>
<th>Stage IV</th>
<th>Child-Pugh B (CP-B)</th>
<th>800 mg Sor initial dose</th>
<th>Average dose (mg/day)</th>
<th>Sor therapy duration (wks)</th>
<th>Treatment emergent serious AEs</th>
<th>Deaths*</th>
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<tr>
<td>Total n (%)</td>
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<td>479</td>
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<td>134 (28)</td>
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<td>Hep/Gl</td>
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<td>168 (35)</td>
<td>78 (46)</td>
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<td>109 (65)</td>
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<td>59 (36)</td>
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* Treatment emergent and up to 30 days after last dose.
Emerging Trends; Treatment of Advanced HCC:

- New molecular target agents
- New combination treatment
- Exploring alternative treatment
### Molecular Target Agents in HCC: overview

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<th>VEGF</th>
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</table>

Sources: Trial Trove, ClinicalTrials.gov (NCI), Evaluate Pharma, IMS Knowledge Link, Espicom, IDdB3, BioPharm Insight, MedTrack
Phase III randomized trial of brivanib vs sorafenib in advanced HCC

Eligibility criteria
- Advanced HCC
- Child-Pugh A
- PS 0 or 1

Randomization 1:1

Sorafenib

Brivanib

Primary outcome
- OS

Secondary outcomes
- TTP
- OCR
- DCR
- TTR
- Safety

N = 1,050

Available at: www.clinicaltrials.gov. NCT00858871.
Chest CT (10.4.30)

f/u Chest CT (10.6.29)
Emerging Trends; Treatment of Advanced HCC:

- New molecular target agents
- New combination treatment
- Exploring alternative treatment
Challenge in advanced HCC

Adavanced HCC (Stage IVa)
- HAIC
- Radiation therapy; internal, external
- Combined therapy or multidisciplinary approach
- Systemic therapy?

HCC with extrahepatic metastasis (Stage IVb)
- Systemic therapy (FOLFOX ?)
Fig. 4. Treatment algorithm for HCC (cited from [3], with permission). a Presence of vascular invasion or extrahepatic metastasis to be indicated separately. b Selected when the severity of damage is class B and the tumor diameter is no greater than 2 cm. c Tumor diameter should be no greater than 5 cm when there is only one tumor.
Repetitive Short-Course Hepatic Arterial Infusion Chemotherapy With High-Dose 5-Fluorouracil and Cisplatin in Patients With Advanced Hepatocellular Carcinoma

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BACKGROUND. Hepatic arterial infusion chemotherapy (HAIC) has often been selected as a therapeutic option for patients with advanced hepatocellular carcinoma (HCC). The objective of the current study was to evaluate the efficacy and safety of repetitive HAIC with high-dose 5-fluorouracil (5-FU) and cisplatin given for 3 days in patients with advanced HCC.

METHODS. Between January 2001 and December 2004, a total of 41 patients with unresectable advanced HCC were enrolled. The patients underwent HAIC via the implantable port system with 5-FU (at a dose of 500 mg/m² on Days 1–3) and cisplatin (at a dose of 60 mg/m² on Day 2) every 4 weeks. Tumor response was assessed at the end of every 3 cycles.

RESULTS. The median age of the patients was 53 years and 34 patients (82.9%) had evidence of portal vein thrombosis. In total, 230 cycles of HAIC were administered to the 41 patients, with a median of 6 cycles given (range, 1–14 cycles). Nine patients (22.0%) achieved a partial response and 14 patients (34.1%) had stable disease. The median time to disease progression and overall survival were 7.0 months and 12.0 months, respectively. The overall survival was found to be significantly longer in the successful disease control group (patients with a complete response, partial response, and stable disease) than in the disease progression group (median of 14.0 months vs 6.0 months; P < .001). Adverse reactions were tolerable and successfully managed with conservative treatment.

CONCLUSIONS. HAIC with high-dose 5-FU and cisplatin given for 3 days achieved effective and safe results in patients with advanced HCC. Therefore, repetitive short-course HAIC with high-dose 5-FU and cisplatin may be useful as an alternative therapeutic option for patients with advanced HCC. Cancer 2007;110:129–37. © 2007 American Cancer Society.
Hepatic Artery Infusion Chemotherapy

A randomized comparative study of high-dose and low-dose hepatic arterial infusion chemotherapy for intractable, advanced hepatocellular carcinoma

- Prospective randomized multicenter study
- 68 advanced HCC
- Same regimen
  - 5-FU (500mg vs 170mg)
  - Cisplatin (60mg vs 7mg)
- Hepatic artery infusion (HAIC) by port system
- Objective res: 39%

Woo & Bae et al Cancer Chemother Pharmacol 2010
A comparative study of high-dose HAIC and TACE using doxorubicin for intractable, advanced HCC

CONCLUSIONS:
High-dose HAIC appears to improve the tumor response and survival outcome compared to conventional TACE using doxorubicin in patients with intractable, advanced HCC.

Kim et al. Korean J Hepatol. 2010
Radiotherapy Technology

- Image Guided RT
- Proton RT
- CyberKnife
- G-Knife
- Conventional RT
- Conventional RS

Radiotherapy (RT)  Radiosurgery (RS)

Technology evolved to precision RT
간동맥 색전술 실패 후 방사선 치료→암크기는 비슷하나 괴사→수술해 보니 90% 괴사

- 2010.01.25
- 2010.09.13
Case; HCC with PVT, CCRT with 50 Gy/20 fr.
고가 최첨단 암치료기 만능? 알고 써야 값만큼 효과

-과학기술의 총아, ‘노발리스티엑스’

사이버나이프와 래피드아크가 결합된 방사선치료기. 노발리스티엑스는 한마디로 가장 정밀하고, 가장 안전하게 암환자를 치료하는 현존 최고의 제일 스마트한 암치료기다.
최첨단 치료법의 치료효과

• 치료장비의 특장점 파악 및 효과 극대화와 합병증 최소화하는 치료법 고안 및 적용
• 숙련된 장비 사용 전문가 양성
• 축적된 임상자료를 통한 적절한 치료대상 환자의 선택
• 임상의사와 방사선종양 전문가와의 협력
MMP-9 as a key factor of radiation-induced HCC invasiveness

Cheng et al., Oncogene 2006
Multimodality Treatments

Since single Tx for HCC is still unsatisfactory, the attempt of multimodality strategy is logical

- Neoadjuvant therapy
- Combined therapy
- Multistep therapy
Converted to Resection after CCRT

M/51, 16 cm, T4N0, PVT

1 mo

15 mo, path: 100%

M/53, 11 cm, T3N0

Initial

post-CCRT

pre-OP
Pilot Clinical Trial of Localized Concurrent Chemoradiation Therapy for Locally Advanced Hepatocellular Carcinoma With Portal Vein Thrombosis

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3 Department of Diagnostic Radiology, Yonsei Liver Cancer Special Clinic, Yonsei Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea.

1-yr survival: 57.6%
2-yr survival: 32.2%
3-yr survival: 24.1%
Median: 13.1 mo
Mean: 18.2 mo
HCC with PVTT-multidisciplinary Tx involving radiotherapy-1

- IA 5-FU (500mg/d)
- IA 5FU(750mgx3d)+ IA DDP(60-90mg)
- Radiotherapy (45 Gy/5 wks)

CT
Angiography
R15
αFP

Dx
2nd month
End of Tx response

CT
Radiotherapy
IA 5-FU
IA 5FU
IA DDP

End ofTx response

2nd month
6th month

CCRT response
**Table 2. Comparisons of Baseline Clinical Characteristics According to Maximal Tumor SUV**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Maximal Tumor SUV &lt;6.1, n=53</th>
<th>Maximal Tumor SUV ≥6.1, n=54</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.1 ± 10.9</td>
<td>51.6 ± 10.6</td>
<td>.101</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>45 (84.9)</td>
<td>44 (81.5)</td>
<td>.636</td>
</tr>
<tr>
<td>ECOG, 0:1</td>
<td>31:22</td>
<td>26:28</td>
<td>.284</td>
</tr>
<tr>
<td>White blood cell count per μL</td>
<td>6430 ± 2137</td>
<td>6313 ± 2650</td>
<td>.853</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.4 ± 1.61</td>
<td>13.7 ± 1.23</td>
<td>.376</td>
</tr>
<tr>
<td>Platelet count, 10^3/μL</td>
<td>186 ± 84</td>
<td>219 ± 98</td>
<td>.064</td>
</tr>
<tr>
<td>Prothrombin time, INR</td>
<td>1.049 ± 0.150</td>
<td>1.069 ± 0.102</td>
<td>.421</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>0.97 ± 0.61</td>
<td>0.80 ± 0.43</td>
<td>.110</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>4.1 ± 0.47</td>
<td>4.0 ± 0.43</td>
<td>.457</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>112 ± 54.8</td>
<td>94 ± 58.5</td>
<td>.452</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>73.2 ± 38.9</td>
<td>44.9 ± 32.7</td>
<td>.052</td>
</tr>
<tr>
<td>AFP, ng/mL</td>
<td>7313 ± 1787</td>
<td>15440 ± 2200</td>
<td>.040</td>
</tr>
<tr>
<td>PIVKA-II, mAU/mL</td>
<td>1478 ± 752</td>
<td>1243 ± 839</td>
<td>.132</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>32, 60.3%</td>
<td>40, 74.1%</td>
<td>.131</td>
</tr>
<tr>
<td>TNM stage, III:IVA</td>
<td>13:40</td>
<td>12:42</td>
<td>.778</td>
</tr>
<tr>
<td>BCLC stage, B:C</td>
<td>21:32</td>
<td>14:40</td>
<td>.131</td>
</tr>
<tr>
<td>Child-Pugh class, A:B</td>
<td>49:4</td>
<td>52:2</td>
<td>.437</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; PIVKA-II, prothrombin induced by vitamin K absence or antagonist; SUV, standardized uptake value.
Overall survival according to SUVmax

Group 1:
median OS 17.9 months
(95% CI 11.0 – 24.7 months)

Group 2:
median OS 11.3 months
(95% CI 9.7 - 12.9 months)

p=0.013

Kim et al, Cancer. 2011
적절한 치료를 위한 선결조건

• 치료관련 분야별 전문가 양성 및 시설 및 장비 충족
• 치료시작전 치료효과의 득이 실보다 크다는 확신과 치료 후 확인
• 치료대상자가 치료 impossible과 difficult 구별 필요
• 제한된 경험극복을 위한 internal and external communication and cooperation 필요
Team of YLCSC

YLCSC

Medical team
Hepatologist, oncologist

Surgical team
Liver surgeon, transplant surgeon, Pathologist

Radiology team
Diagnostic radiology
Intervention radiology
Radiation oncology
Summary; Optimal treatment in HCC

- Early stage; First choice; Curative efficacy
- Intermediate stage;
  1. Many options according to stage and tx. Response
  2. Try to avoid incomplete tx
- Advanced stage; impossible/difficult
- Impossible; advanced and poor liver function;
To Treat or Not to Treat
Difficult or Impossible to Treat
PET CT (2011.01.04)

NAB (1.5):
Positive for malignancy, metastatic carcinoma

M/52

Difficult or Impossible
Further decrease in size and intensity of FDG uptake in the multiple LNs in the retroperitoneum, hepatoduodenal ligament, retrocrural area, suggestive of favorable treatment response with residual tumor.
Darwin’s evolution & Galapagos
Emerging Trends of Sorafenib: Linking Staging to Treatment

TACE = transarterial chemoembolization; BSC = best supportive care.

How to establish guideline?

- Evidence based guideline; Level of evidence 1; RCT
- Clinical experienced based guideline; Level of evidence 2,3; case control
Treatment Algorithm for Intermediate and Advanced HCC in Asia
Asian Consensus Workshop Report:
Expert consensus guideline for the management of intermediate and advanced hepatocellular carcinoma in Asia

• In the first APPLE meeting, the significant different distribution of intermediate and advanced stage HCC was recognized among Asian countries. Furthermore, the significant differences in the treatment approach according to HCC stages were also identified.

• A consensus for managing intermediate and advanced stage HCC cannot be easily drawn due to these disparities in clinical practices and guidelines among Asian countries.

• Thus, new staging system suitable for Asian HCC patients and corresponding optimal treatment algorithm should be further investigated using evidence-based data, which finally make a way to Asian consensus for the management of intermediate and advanced stage HCC.
Thank You for your attention!